Preparation and Structure of an Unexpected Dehydrogenation Product from 2,6-Diphenylcyclohexanone Oxime

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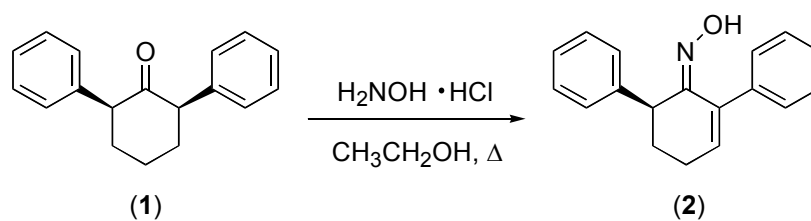
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Index Abstract

An unexpected dehydrogenation product formed in the synthesis of 2,6-diphenylcyclohexanone oxime was characterized and studied by x-ray crystallography, NMR spectroscopy, and computational methods.

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(6*S*)-2,6-diphenylcyclohex-2-enone oxime

Abstract

The synthesis, spectroscopic studies, computational analysis, and crystal structure of (6*S*)-2,6-diphenylcyclohex-2-enone oxime are described. The oxime crystallizes in the monoclinic space group P2$_1$/c with *a* = 11.5269(11) Å, *b* = 6.6724(6) Å, *c* = 19.0105(18) Å, β = 100.863(3)$^{\circ}$, V = 1435.9(2) Å^3, and Z = 4. Semi-empirical (AM1), *ab initio* (MP2/6-31G*), and density functional theory (B3LYP/6-31G*) calculations suggest that there are two low-energy conformations available for the oxime. Significant differences were observed between the dihedral angles in the conformers. Good agreement was found between the crystal data and one of the conformers from the calculations. The absence of certain splitting patterns in the ^{1}H NMR spectrum of the title compound is in contrast to what would be expected on the basis of the dihedral angles and suggests that rapid interconversion is possible in solution. Analysis of the crystal packing suggests that one conformer is favored in the solid state, stabilized by packing interactions. and interconversion is prohibited due to a blocking effect.

Introduction

Oximes and related compounds have found widespread use as drugs and pesticides[1,2] and, as a result, are commonly encountered in the environment. Oxidation of oximes can result in the formation of reactive oxygen species (ROS) such as iminoxyl radicals,[3,4] which are deemed harmful to organisms.[5] It was shown that the in vivo metabolism of cyclohexanone oxime (an intermediate in the synthesis of polycaprolactam or Nylon-6) in rats resulted in excessive nitric oxide (NO) formation, which may be responsible for the toxicity of this compound.[6] Furthermore, cyclohexanone oxime and structurally related oximes have been shown to be animal carcinogens.[7,8] A suggested pathway for the formation of nitric oxide from oximes involves the formation of an iminoxyl radical intermediate.[9] To gain a better understanding of the structure-reactivity relationships in the oxidation of oximes, we have undertaken a study of a series of cyclohexanone oxime derivatives. One of the compounds involved in this study, 2,6-diphenylcyclohexanone, upon reaction with hydroxylamine hydrochloride, underwent an unexpected dehydrogenation reaction to yield an α,β-unsaturated oxime, the crystal structure of which is presented here. The structure obtained from x-ray diffraction is compared to the results of semi-empirical (AM1),[10] density functional theory (B3LYP/6-31G*),[11,12] and *ab initio* (MP2/6-31G*) molecular orbital calculations.[13,14]

Experimental

Instrumentation

Sample analyses were performed on a Hewlett Packard 5890 series II Gas Chromatograph

coupled to a Hewlett Packard 5971 series Mass Selective Detector (MSD) and on a Perkin-Elmer

(PE) Autosystem equipped with a Flame Ionization Detector (FID). The HP GC/MS was

equipped with an HP-5 capillary column (30 m x 0.25 mm i.d.; film thickness: 0.25μm). The PE

GC/FID was equipped with a Chrompack CP-Sil-5-Cb capillary column (30 m x 0.32 mm i.d;

film thickness 0.25μm). The mass spectrum is reported as *m/z* (relative intensity). [1]H and [13]C

NMR spectra were recorded on a Varian Inova 500 instrument. The reported chemical shifts (δ)

are relative to tetramethylsilane. The infrared spectrum was recorded on a Perkin-Elmer 1600

spectrometer and are reported in wavenumbers (cm^{-1}). The melting point was determined using a

Mel-Temp II apparatus (Laboratory Instruments) and is uncorrected.   Calculations were

performed using the computer program Spartan 02 installed on a PowerMac G4.[15]

*Synthesis of (6*S*)-2,6-diphenylcyclohex-2-enone oxime.*

All commercially available chemicals were obtained from Aldrich (Milwaukee, WI). A

100 mL round bottom flask was charged with 2,6-diphenylcyclohexanone (2.52 g, 0.010 mol)

and hydroxylamine hydrochloride salt (1.35 g, 0.019 mol). Aqueous ethanol (50 mL) and three

drops of concentrated HCl were added and the mixture was refluxed for 5 hours. After cooling,

more hydroxylamine hydrochloride (approximately 0.5 g) was added and the mixture was stirred

overnight. The reaction was followed by GC/FID and GC/MS. After completion, the solvent

was removed by rotary evaporation. Water was added to the residue (to dissolve the residual

hydroxylamine hydrochloride) and extracted with ether (three times). The oxime was purified

by column chromatography using a hexanes – chloroform gradient. Recrystallization from methanol yielded compound **2** ((6*S*)-2,6-diphenylcyclohex-2-enone oxime). IR (KB , cm^{-1}): 3216.7 (O-H), 1599.0 (C=N); ^{1}H NMR (CDCl$_3$) δ: 7.58 (s, 1H, H-1), 7.37 – 7.20 (m, 10H, aromatic protons), 6.21 (d, 4.39 Hz, 1H, H-3), 4.73 (s, 1H, H-6), 2.25 – 2.04 (m, 4H, H-4a,b and H-5a,b),; ^{13}C NMR (CDCl$_3$) δ: 157.48, 140.49, 139.37, 137,12, 136.33, 129.02, 128.50, 127.92, 127.32, 127.28, 126.43, 36.62, 28.42, 21.81; Mass Spectra (EI) m/z: 263 (M$^{+\bullet}$, 64%), 246 (40), 244 (53), 218 (35), 168 (56), 154 (17), 142 (35), 128 (32), 115 (100), 103 (31), 91 (45), 77 (35), 63 (16), 51 (23); m.p. 164.0 – 165.5°C.

Crystallography

Crystals were examined in the crystal growth chamber by viewing them under a stereomicroscope equipped with crossed polarizers, and single crystals of appropriate size were mounted to the tip of a 0.1 mm glass capillary with glue. Data were collected from single crystals of each sample at –30˚C on a SMART© 1000 CCD detector system using graphite monochromated Mo Kα radiation. An entire hemisphere of data was collected in multi-run mode with ω as the rotation axis. Detector-to-sample distance was 5.25 cm, and the detector 2θ angle was –28 degrees. Rotation width was 0.3 degrees, frame size was 512 x 512 pixels, number of frames was 1868, data collection time per frame was 60 seconds.

SMART v5.618© was used for data collection, indexing of reflections, and determination of lattice parameters.[16] SAINT+ v6.02© was used for integration of reflection intensities.[17] Absorption corrections were applied using SADABS.[18] SHELXTL v6.10© was used for data reduction, space group determination, structure determination, structure refinement, graphics, and structure reporting.[19] All x-ray crystallographic hardware, including analysis programs and diffraction unit, are copyrights of Bruker AXS, INC.

Results and Discussion

The oxime was prepared using standard conditions from commercially available 2,6-diphenylcyclohexanone (**1**) and analysis of the crude reaction mixture by gas chromatography with flame ionization detection (GC/FID) and mass selective detection (GC/MS) showed the presence of the desired (*cis*) product. However, workup of the mixture followed by recrystallization of the crude product resulted in an unexpected dehydrogenation reaction, giving rise to the formation of (6*S*)-2,6-diphenylcyclohex-2-enone oxime (**2**) rather than the anticipated product. The identity of the product was established by x-ray crystallography (Fig. 1). Details of the structure solution and refinement are presented in Table 1, and atomic coordinates and thermal parameters are reported in Table 2.
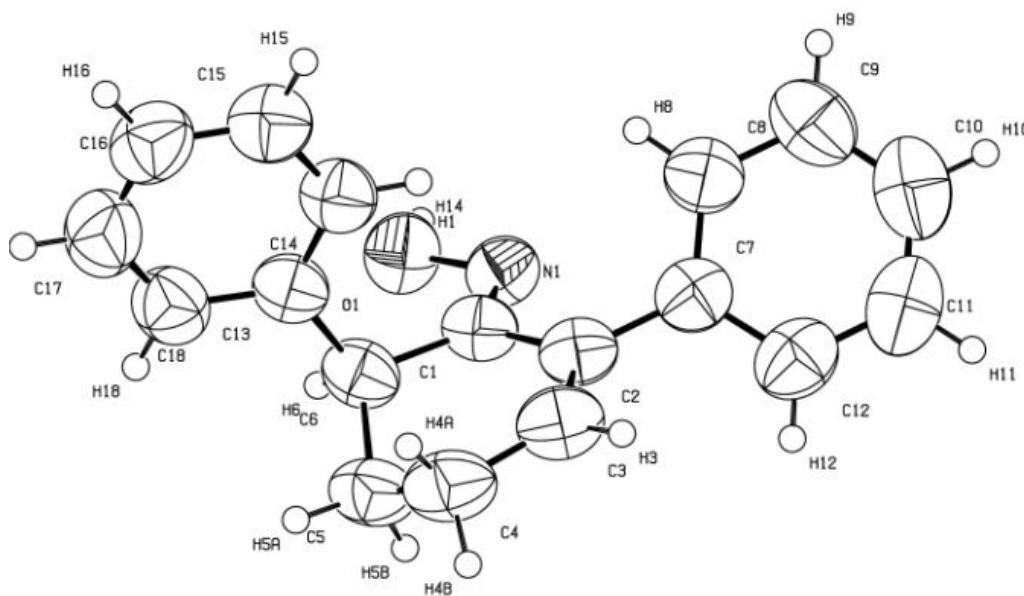

FIGURE 1

Figure 1. An ORTEP drawing of (6*S*)-2,6-diphenylcyclohex-2-enone oxime (**2**) with the atom numbering scheme. Thermal ellipsoids are plotted at the 50% probability level.

The structure was confirmed by NMR, IR, and MS spectroscopy. The hydroxyl proton (H-1) is found at δ 7.58 ppm, in agreement with a previous study on similar compounds.[20] The olefinic proton (H-3; δ 6.21 ppm) shows a small coupling constant (^3J = 4.4 Hz) which is also found in the multiplet at δ 2.25-2.04 ppm. Analysis of the crystal structure data indicates that a coupling of this magnitude is most likely to occur with H-4b. The benzylic proton (H-6) is found at δ 4.73 ppm, however, no splitting is observed. This is somewhat unexpected. On the basis of the dihedral angles between H-6 and H-5a (-66°) or H-5b (52°) obtained from the crystal structure, coupling constants of approximately 2.2 Hz and 3.7 Hz would be expected. Calculations were performed at varying levels of theory to further elucidate this observation. AM1 calculations suggest that there are two low-energy conformers (Table 3), and results indicate that conformer 2 shows a much better agreement between the crystal structure and the calculated bond lengths and angles than conformer 1. The differences between these two conformers are clearly visible in Figure 2.

For conformer 1, most of the calculated dihedral angles involving C(3), C(4), C(5), C(6), and the attached hydrogens are significantly different from those observed in the crystal. Although the calculated dihedral angles between H-6 and H-5a or H-5b, as well as those between H-3 and H-4a or H-4b of conformer 2, are in much better agreement with those obtained from the crystal structure, much larger values for the coupling constants than those observed would be expected from these geometries. These results suggest that in solution both low-energy conformers are present and can rapidly interconvert. The calculated energy difference between the two conformers (Table 4) is small and although the barrier for interconversion is unknown,
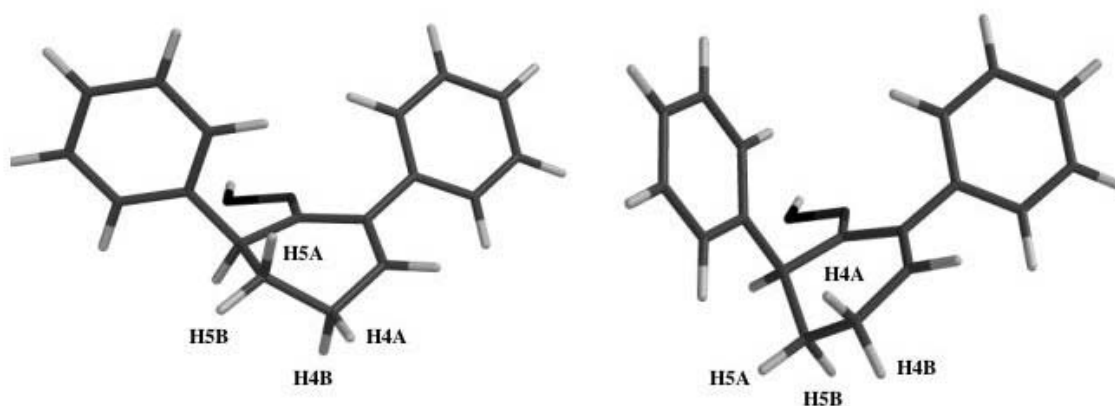
FIGURE 2

Figure 2. Calculated (MP2/6-31G* minimized) structures of the two lowest energy conformers of (6*S*)-2,6-diphenylcyclohex-2-enone oxime showing the differences in dihedral angles of the cyclohexene moiety (carbons 4, 5, and 6), as well as the orientation of the phenyl ring attached to C(6).

we believe it should be less than that of a typical ring-flip in cyclohexane (< 10 kcal/mol). Such

a barrier would allow interconversion between the conformers to take place rapidly at room

temperature, and this interconversion could lead to a disappearance of certain coupling constants.

There are additional features in the structure that likely result from crystal packing

effects, the first being the orientation of one of the phenyl groups. As can be seen from the data

listed in Table 3, all the calculated values of the dihedral angle C(1) – C(2) – C(7) – C(8) are in

good agreement with the actual value obtained from the crystal structure. There is a significant

difference, however, between the calculated and actual dihedral angles C(1) – C(6) – C(13) –

C(14). The orientation of this particular phenyl group may be a result of crystal packing. Figure

3 shows that the orientation of these particular phenyl rings is determined by the methylene

groups (C(4) and C(5)) of two different molecules. Crystal packing also reveals the existence of

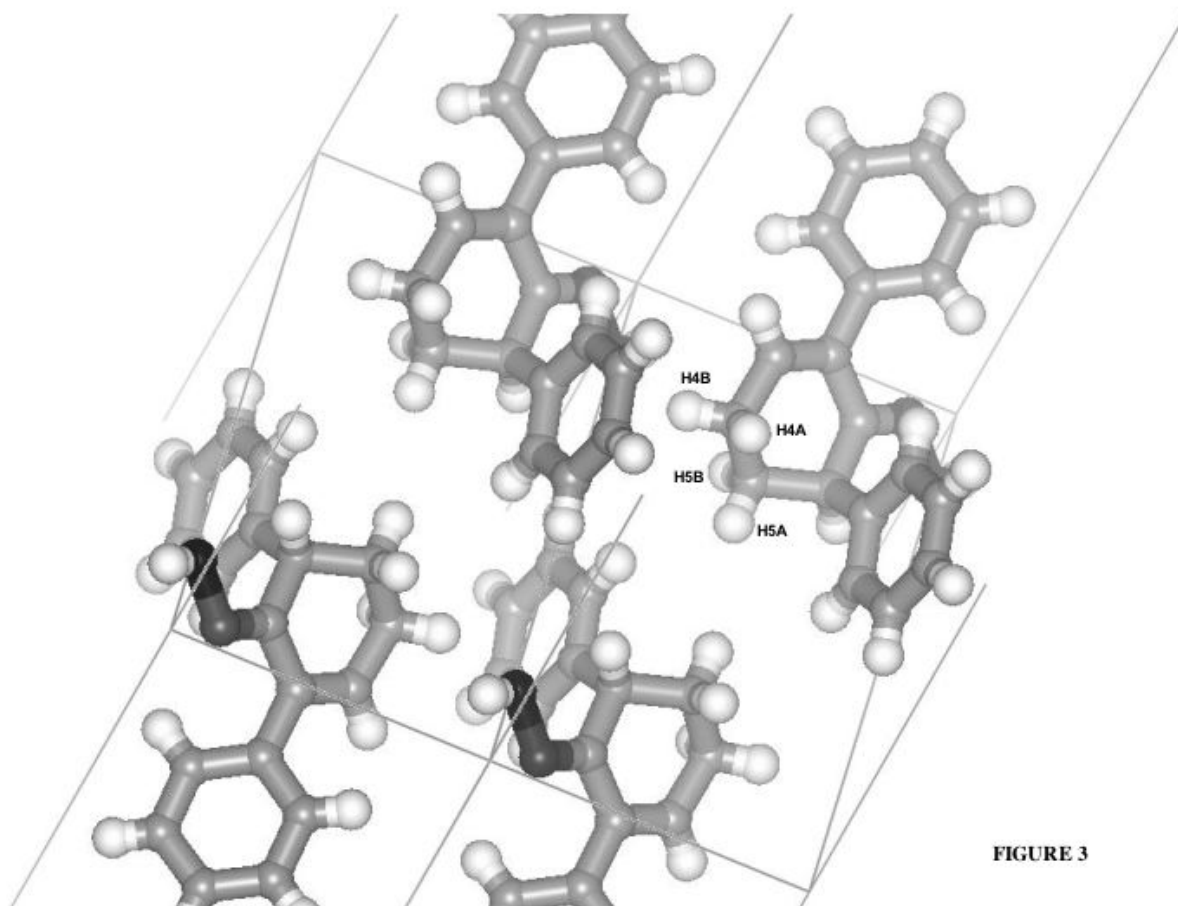hydrogen bonds between two oxime moieties in adjacent unit cells (Figure 4).

FIGURE 3

Figure 3. Crystal packing diagram showing the interaction between the phenyl ring attached to
C(6) and the methylene groups (C(4) and C(5)) of two other oxime molecules.
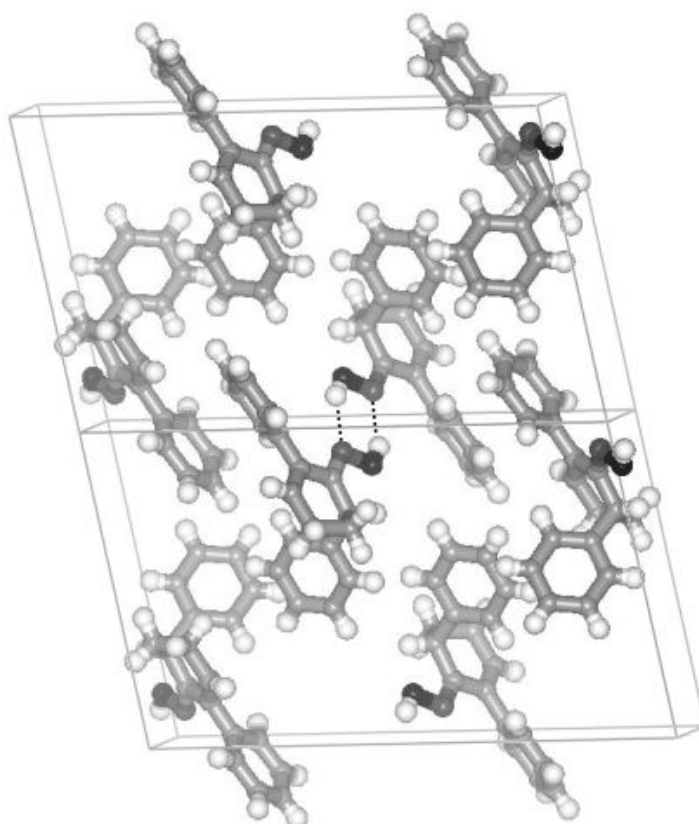
FIGURE 4

Figure 4. Crystal packing diagram showing the presence of hydrogen bonds between two oxime molecules.

These results suggest that the physical environment (i.e., solid state, solution, or gas phase) has a dramatic effect on the conformation of cyclohexanone oximes, and therefore, could potentially influence the reactivity of these compounds. Further experiments with other substituted cyclohexanone oximes are currently underway.

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Table 1. Crystal Data for Compound **2**.

Compound	$C_{18}H_{17}NO$
CCDC no.	214942
Formula weight	263.33
Temperature, K	293
Wavelength, Å	0.71073
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions, Å	$a = 11.5269(11)$, $\alpha = 90^o$
	$b = 6.6724(6)$, $\beta = 100.863(3)^o$
	$c = 19.0105(18)$, $\gamma = 90^o$
Volume, Å^3	1435.9(2)
Z	4
Density (calculated), Mg/m^3	1.218
Absorption coefficient, mm^{-1}	0.075
$F(000)$	560
Theta range for data collection, ^{o}	1.80-23.30
Index ranges	$-11 \geq h \geq 12$
	$-7 \geq k \geq 7$
	$-21 \geq l \geq 20$
Reflections collected	8680
Independent reflections	2074
Rint	0.0313
Data/restraints/parameters	2074/0/183
Goodness-of-fit on F^2	1.127
Final R indices $[I > 2\sigma(I)]$	$R1 = 0.0679$, $wR2 = 0.2003$
R indices (all data)	$R1 = 0.0833$, $wR2 = 0.2288$
Extinction coefficient	0.039(9)
Largest diff. peak and hole, e Å^{-3}	0.30 and -0.19

Table 2. Atomic Coordinates and Their Equivalent Isotropic Thermal Parameters for Compound **2**.

Atom	x	y	z	U_{eq}
O(1)	0.13689(15)	0.0081(3)	-0.00950(11)	0.0794(7)
N(1)	0.09129(17)	0.1496(3)	0.03318(11)	0.0680(7)
C(1)	0.1658(2)	0.2892(4)	0.05575(12)	0.0651(7)
C(2)	0.1288(2)	0.4467(4)	0.10214(13)	0.0688(7)
C(3)	0.1985(3)	0.6072(4)	0.11896(16)	0.0823(9)
C(4)	0.3090(3)	0.6466(4)	0.09200(17)	0.0905(10)
C(5)	0.3161(3)	0.5241(4)	0.02658(17)	0.0860(9)
C(6)	0.2861(2)	0.3038(4)	0.03665(14)	0.0716(8)
C(7)	0.0180(2)	0.4245(4)	0.13065(13)	0.0727(8)
C(8)	-0.0093(2)	0.2473(5)	0.16312(14)	0.0808(8)
C(9)	-0.1095(3)	0.2341(6)	0.19392(17)	0.0986(10)
C(10)	-0.1823(3)	0.3964(7)	0.1929(2)	0.1067(12)
C(11)	-0.1569(3)	0.5722(6)	0.1616(2)	0.1034(11)
C(12)	-0.0580(3)	0.5864(5)	0.13062(16)	0.0883(9)
C(13)	0.3817(2)	0.2014(4)	0.09131(14)	0.0695(7)
C(14)	0.3692(2)	0.1496(4)	0.15985(15)	0.0767(8)
C(15)	0.4606(3)	0.0608(5)	0.20711(17)	0.0872(9)
C(16)	0.5663(3)	0.0218(5)	0.1865(2)	0.0953(10)
C(17)	0.5799(3)	0.0707(5)	0.1188(2)	0.0993(11)
C(18)	0.4893(2)	0.1593(5)	0.07157(18)	0.0859(9)

Table 3. Selected Bond Lengths [Å], Angles [°] and Dihedral Angles [°] for Compound **2**.

	Crystal	AM1		MP2/6-31G*		B3LYP	
Conformer		**#1**	**#2**	**#1**	**#2**	**#1**	**#2**
N(1) – O(1)	1.410(3)	1.313	1.316	1.411	1.417	1.402	1.410
C(1) – N(1)	1.285(3)	1.312	1.312	1.301	1.300	1.291	1.289
C(1) – C(2)	1.485(4)	1.482	1.479	1.472	1.471	1.481	1.480
C(1) – C(6)	1.501(3)	1.518	1.519	1.515	1.508	1.530	1.525
C(2) – C(3)	1.341(4)	1.348	1.346	1.356	1.356	1.351	1.351
C(2) – C(7)	1.486(3)	1.462	1.465	1.478	1.481	1.490	1.491
C(3) – C(4)	1.483(5)	1.482	1.477	1.502	1.498	1.504	1.501
C(4) – C(5)	1.503(4)	1.516	1.514	1.530	1.526	1.533	1.533
C(5) – C(6)	1.530(4)	1.526	1.526	1.537	1.542	1.546	1.535
C(6) – C(13)	1.526(4)	1.500	1.498	1.515	1.525	1.528	1.537
O(1) – N(1) – C(1)	112.3(2)	117.0	116.7	110.4	111.2	112.0	112.4
N(1) – C(1) – C(2)	117.6(2)	118.0	118.8	116.0	116.5	115.8	116.7
C(1) – C(2) – C(3)	118.7(2)	118.7	120.4	117.9	119.7	118.6	119.4
C(1) – C(2) – C(7)	120.6(2)	119.1	118.9	120.0	119.9	120.2	120.3
C(1) – C(6) – C(5)	109.5(2)	113.9	109.7	111.8	107.5	112.2	107.9
C(1) – C(6) – C(13)	112.8(2)	110.5	110.9	110.6	109.7	113.1	111.4
C(2) – C(3) – C(4)	125.0(3)	120.7	124.6	121.2	124.0	122.7	124.9
C(3) – C(4) – C(5)	111.9(3)	109.7	114.0	108.7	111.4	109.7	112.1
C(4) – C(5) – C(6)	111.7(2)	112.8	114.9	111.8	111.6	112.6	112.6
O(1) – N(1) – C(1) – C(2)	-179.3(2)	176.3	179.5	176.4	-178.0	174.9	-179.9
N(1) – C(1) – C(2) – C(3)	-171.7(2)	-143.8	-156.0	-151.5	-168.5	-154.2	-165.5
N(1) – C(1) – C(6) – H(6)	25.8	44.0	17.4	53.4	21.3	57.5	20.9
C(1) – C(2) – C(3) – C(4)	3.0(4)	-4.1	-2.1	-1.5	2.3	-2.3	2.5
C(1) – C(2) – C(7) – C(8)	47.9(3)	44.1	50.0	45.0	53.5	46.2	50.3
C(1) – C(6) – C(13) – C(14)	-17.0(4)	-55.4	58.8	-52.1	34.8	-52.0	42.3
C(2) – C(3) – C(4) – C(5)	17.9(4)	-39.7	7.9	-39.8	15.7	-35.2	13.5
C(3) – C(4) – C(5) – C(6)	-47.6(3)	55.4	-33.4	59.0	-47.3	55.1	-44.0
C(4) – C(5) – C(6) – C(1)	56.4(3)	-29.3	51.4	-38.1	60.0	-39.0	57.1
H(3) – C(3) – C(4) – H(4a)	76.7	17.7	63.4	17.4	71.6	22.4	69.4
H(3) – C(3) – C(4) – H(4b)	-41.1	-100.4	-51.9	-100.4	-44.0	-94.5	-45.2
H(5q) – C(5) – C(6) – H(6)	-65.8	-150.4	-68.5	-160.7	-58.9	-162.4	-63.0
H(5b) – C(5) – C(6) – H(6)	52.1	-33.5	47.2	-44.2	57.0	-46.3	52.4

Table 4. Relative (calculated) energies (kcal mol^{-1}) for the two low-energy conformers of compound **2**.

	Conformer 1	Conformer 2
AM1	0.0	+0.17
MP2/6-31G*	0.0	-1.60
B3LYP/6-31G*	0.0	-0.84